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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/833,506	04/07/1997	ROBERT WEBBER	14291	2615

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/833,506	WEBBER, ROBERT	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed on 12/27/05 has been considered. Applicant's arguments are deemed to be persuasive-in-part.

Claims 82-105 are pending.

Claims 1-81 and 106 are cancelled.

The rejection over claims 82-83, 86-88, 103 and 106 under 35 U.S.C. 102(b) as being anticipated by Moncada et al WO 94/23038 or Kobzik et al Am. J. Respir. Cell Mol. Biol. vol. 9 p. 371 (1993) or Fujisawa et al J. Neurochemistry vol. 64 p. 85 (1995) is withdrawn after reconsideration.

The rejection of claims 82, 86-88, 103 and 106 under 35 U.S.C. 102(b) as being anticipated by Ikeda Tojo Medical Journal vol. 65 p. 433 (6/95) is withdrawn after reconsideration.

Response to Arguments/New Grounds of Rejection

Sequence listing

On page 32 the sequence at region 25-42 needs a SEQ ID No.

Applicant states that SEQ ID NO. 29 covers region 25-42. Seq ID NO. 29 covers 37-54 not 25-42.

Claim Rejections - 35 USC § 112

Claims 82-105 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Item "c" from the previous action is withdrawn in view of applicant's amendment. Items "a" and "b" remain and are reiterated below.

a. In claim 83, what does applicant mean by "polymer mimicking an artificial antibody" and "phage display binding sites"? Polymers are polymers (organic compounds) not antibodies.

Applicant argues that both terms "are intended to leave the conventional meanings in art of biochemistry". If the "leave" the conventional meaning, then they are different from what is in the art and what does applicant intend them to be?

b. In claims 84-85 and 95, the third sequence needs a SEQ Id No.

Applicant states that SEQ ID NO. 29 covers region 25-42. Seq ID NO. 29 covers 37-54 not 25-42.

c. In claim 82, the phrase "binding monoclonal antibody" is confusing. A monoclonal antibody inherently binds or is applicant trying to distinguish this from a non-binding antibody?

d. In claim 83, it is no clear how the oligonucleotide (when it is the binding entity) recognizes human iNOS protein. An oligo cannot bind to a protein.

e. In claims 84 and 85 and 95, there is no antecedent basis for "said region".

f. In the claims the phrase "selected from the group consisting essentially of" is an improper Markush group. The proper phrasing is --selected from the group consisting of--.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 82-106 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No.6531578. The reasons for this rejection are of record in the previous action.

The terminal disclaimer does not comply with 37 CFR 1.321(b) and/or (c) because: it does not state the owner or the percentage of ownership.

Claim Rejections - 35 USC § 112

Claims 83, 85, 89-102, 104 and 105 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There are three parts to this written description rejection.

Part 1

The claims are drawn to specific binding entities comprising the peptide analogues of Tables IX or VII or having Seq ID NO. 89 and 120. While the amino acid sequence of the specific sequences in Tables VII, IX and SEQ ID NO. 89 and 120 are adequately described in the specification as-filed, thereby providing an adequate basis for said peptides; there is insufficient written description as to the identity of a specific binding entity having or comprising said specific peptides that would still maintain the function of the peptide. Consequently, the specification does not provide an adequate written description of specific binding entities having or comprising said peptides.

The specification as filed does not provide adequate written description support for specific binding entities having or comprising said specific peptides. Polypeptides having diverse functions are encompassed by said terminology. For example, a specific binding entity comprising the peptide analogues of Table VII or IX would include polypeptides comprising the peptides of the table with an amino acid sequence on either said of said peptide with undetermined length and composition. Similarly, a peptide having SEQ Id No. 89 would read on a polypeptide having Seq ID No 89 with an amino acid sequence on either said of said peptide with undetermined length and composition. Thus a broad genus having potentially highly diverse functions is encompassed by the claims and conception cannot be achieved until reduction to

practice has occurred, regardless of the complexity or simplicity of the method. For example, Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2). Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Part 2

The claims are drawn to binding entities selected from the group consisting of oligonucleotides, polymers mimicking artificial antibodies and phage displayed binding sites. While the amino acid sequence of the specific sequences in Tables VII, IX and SEQ ID NO. 89 and 120 are adequately described in the specification as-filed, thereby providing an adequate basis for said peptides; there is insufficient written description as to the identity of a specific binding entity being oligonucleotides, polymers mimicking artifical antibodies and phage displayed binding sites. Consequently, the specification does not provide an adequate written description of said specific binding entities.

The specification as filed does not provide adequate written description support for said specific binding entities. For example, the specification provides no nucleic acid sequences for oligonucletoides that would bind to human iNOS, nor does the specification state what these oligos would encode. As for the polymers mimicking artificial antibodies, the specification provides no description of the antibodies that would interact with human iNOS, much less artificial antibodies or mimics thereof. As for the phage display binding sites, there is also no description. Thus a broad genus having potentially highly diverse functions is encompassed by the claims and conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Part 3

The claims are drawn to binding entities reactive with mimics of human iNOS. While the human iNOS is adequately described in the specification as-filed, thereby providing an adequate basis for human iNOS; there is insufficient written description as to the identity of a mimic of human iNOS. Consequently, the specification does not provide an adequate written description of a mimic of human iNOS.

The specification as filed does not provide adequate written description support for a mimic of human iNOS. For example, the specification provides no description of what the mimic should be composed of (amino acids, organic groups, sugars). Are there core structures that need to be retained in the mimic? Not only is the concept of the mimic required, but the conception cannot be achieved until reduction to practice has occurred.

Therefore, only the specifically mentioned peptides meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 82, 86-88 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moncada et al WO 94/23038 in view of Maier, Biochem. Biophys. Acta vol. 1208 p. 145 (9/21/94), Harlow and Lane, "antibodies 91988) p. 72-76 and Marsden et al FEBS Letts vol. 307 p. 287 (8/92) or Nakane et al FEBS Letts vol. 316 p. 175 (1993) or Geller et al PNAS vol. 90 p. 3491 (4/93).

WO 94/23038 dislcoses the use of an antibody specific for NOS in the detection and diagnosis of NOS-mediated disease (page 9-last paragraph). The form of NOS used in iNOS (page 3, lines 3-4). The antibody can be monoclonal (page 10). The assay used include Western Blotting, ELISA's and immunohistochemical assays (page 11-12). In the immunohistochemical assay, the tissue sample is from patients (ie humans) (page 12).

The only difference between the instant invention and the reference is the lack of cross-reactivity of NOS isozymes.

Maier et al disclose that there is 67-71% homology between the inducible and constitutive forms of NOS (page 148, first full paragraph) and cites references 6-11. Marsden et al and Nakane et al are two of these references. Both of these references disclose the aminoa cid sequences of Cnos(Marsden et al discloses eNOS and Nakane discloses nNOS) and it is clear from these references that the carboxy-terminus of the cNOS is different from the iNOS of Maier et al.

Geller et al teach that the C-terminus of mouse and human iNOS are difference (see figure 1).

Harlow and Lane teach that once the DNA sequence is known, there are enormous benefits in making antibodies (page 73). This reference even states that the reasonable order for choosing an immunogen is using the C-terminus and that the size of the peptide should be at least 6 amino acids in length (page 76).

Therefore in view of the suggestion in Harlow and Lane to make antibodies to the carboxy terminus and to use immunogens that are at least 6 amino acids long and in view of the fact that Maier et al discloses that there is little homology between cNOS and iNOS and from Marsden et al and Nakane et al it is clear that the carboxy-terminus of cNOS and iNOS are different, it would have been obvious to one of ordinary skill in the art at the time of the invention to make the monoclonal antibodies of the primary reference directed against the carboxy terminus to avoid the detection of cNOS and thereof acheiving a more sensitive assay.

A rejection similar to this was made in the parent application and was overcome by filing a 131 declaration. Re-submitting the declaration in this application will overcome this art rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesdays and Thursdays from 5:30am to 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheela J Huff
Primary Examiner
Art Unit 1643

sjh